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BIOMATERIALS

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REACTION-BONDED BIORESORBABLE COMPOSITE MATERIAL

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A series of composite materials based on dicalcium phosphate dihydrate and bioactive glass 50S25N5P with physiologically safe pH and compression strength from 4 to 22 MPa has been developed. The composites obtained are resorbable and can be used in trauma treatment and bone tissue disease.

Key words: bioactive glass, low-temperature ceramic, reaction-bonded material, dicalcium phosphate dihydrate, â-tricalcium phosphate, biocomposite.

The diversity of synthetic bone-restoration materials on the world market is growing unabatedly. According to the data on Bone Graft Substitutes — Global Pipeline Analysis, Competitive Landscape and Market Forecast to 2017 the growth rate of profits from synthetic materials on the world market from 2003 to 2010 increased by 7.75%, and it is predicted that the rate of growth will increase by 10% from 2010 to 2017. New technological approaches in traumatology make it possible to solve the problem of ununited fractures, complications after serious trauma and unstable osteosynthesis.

Calcium phosphate implantation materials are most widely used in bone-plastic surgery, since bone tissue is a composite material based on highly disperse carbonate containing hydroxyapatite $Ca_{8.3}(PO_4)_{4.3}(CO_3)_x(HOP_4)_y(OH)_{0.3}$ (CHA) and collagen protein. The composition of calcium phosphate materials is represented by phases of hydroxyapatite (HA), tricalcium phosphate (TCP), dicalcium phosphate dihydrate (DCPD) as well as di- and polyphosphates (PP); the material can contain the indicated phases as a monomineral or in the form of polymineral compositions.

Brushite-containing calcium phosphate materials comprise the final phase of crystallization of DCPD ($CaHPO_4 \cdot 2H_2O$) — they possess good biocompatibility and bioactivity, are nontoxic and easy to prepare; used in the form of cement the material can be introduced directly into the wound zone, permits shaping the article in the course of surgical intervention and eliminating pinning systems. The main advantage of the DCPD-based materials is a high rate of resorption, which makes it possible for them to activate a synthetic capability of osteogenic cells and set the bone restoration process. Two drawbacks of the compound are its acidic nature, which causes the pH in the body to decrease from 7.4 to 3.5, and low strength, which prevents wide use of such materials.

Other osteo inductive, resorption-capable materials are bioactive alkali glasses. Bioactive glass is an amorphous material, obtained in the silicate systems SiO_2–CaO–P_2O_5–X_2O, where X = Na, K, or calcium-phosphate systems CaO–P_2O_5–X_2O with the addition of the oxides MgO, ZnO, Al_2O_3, Ag_2O, TiO_2, MnO, Fe_2O_3, BaO, SrO and CaF_2. The bioactivity of the glass is due to the formation of carbonate hydroxyapatite on its surface in the physiological media of the body (*in vivo*) and in salt buffer solutions (*in vitro*). A strong, osteoid-type tissue forms in the process of bonding of the bone tissue with the surface of bioactive glass via a CHA layer. Silicate glasses are unique in that they have the capability of activating growth and differentiation of osteoid- and fibrous-type cells owing to the content of silicon compounds in the material. *In vitro* [1] and *in vivo* [2] studies have shown that the introduction of silicon into the structure of calcium phosphates increases the biological response and improves new formation of bone tissue. It has been established that under *in vitro* conditions [3] the precipitation of

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soluble silicates, phosphates and ions of calcium activates the genes and controls the cell cycle of osteoblasts.

We have established that the introduction of alkali silicates and granules of bioactive glass into brushite cement compositions increases the pH of the contact medium of the composite material obtained [4], but in the process the strength is degraded.

In the present work our aim was to obtain on the basis of DCPD and bioactive glass composite materials with enhanced strength corresponding to the strength of spongiform bone (1 – 20 MPa in compression), pH close to physiological values and high resorption rate.

Since the ultimate strength of materials decreases exponentially with increasing porosity, a decrease of the initial porosity during pressing of the material increases strength. Such materials, obtained by a low-temperature technology, are said to be reaction-bonded or low-temperature ceramic.

MATERIALS AND METHODS

DCPD cement was obtained in the course of an acid – base interaction of β-tricalcium phosphate β-$Ca_3(PO_4)_2$ and monocalcium phosphate monohydrate $Ca(H_2PO_4)_2 \cdot H_2O$ (MCPM) in the ratio β-TCP : MCPM = 60 : 40%[4] in the reaction

$$\beta\text{-}Ca_3(PO_4)_2 + Ca(H_2PO_4)_2 \cdot H_2O + 7H_2O \rightarrow 4CaHPO_4 \cdot 2H_2O.$$

Precipitated hydrated β-TCP, obtained by the method of [5] and fired for 4 h at 1200°C (high-temperature form) and 900°C (low-temperature form), was used to obtain the cement.

The filler in the composite material (CM) consisted of alkaline bioactive glass in the system Na_2O–CaO–SiO_2–P_2O_5 with the following composition (%): 25 Na_2O, 20 CaO, 50 SiO_2 and 5 P_2O_5. The glass was smelted in a gas furnace at temperature 1400°C, poured off and then fired at 500°C for 1 h; amorphous (a) glass was obtained. Additional heat-treatment of the resulting glass at 800°C for 1 h gave crystallized (c) glass. Separate comminution of amorphous and crystallized glasses was conducted to 10 – 80 μm granules with average size 30 – 40 μm. The filler was introduced in amounts 0, 10 and 20% of the mass of the cement powder. Systems based on low- and high-temperature β-TCP were studied: low — 900-0, 900-10a, 900-20a, 900-10c, 900-20c and high — 1200-0, 1200-10a, 1200-20a, 1200-10c and 1200-20c.

Since the nitrate ions prevent aggregation of the particles, which improves the distribution, and improves strength because the cement stone crystals are smaller, a solution of citric acid with concentration 5 mMole/liter served as the liquid mixed with the composition material [6]. This makes the cement mixture workable at low water/solids (W/S) ratios, and also makes it possible to obtain uniform pressed samples with high strength.

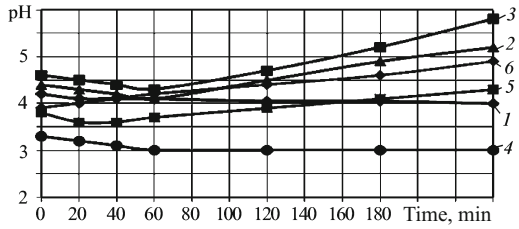

Fig. 1. pH change in the contact medium of composites over time: *1*) 900-0; *2*) 900-20a; *3*) 900-20c; *4*) 1200-0; *5*) 1200-20a; *6*) 1200-20c.

To obtain composite materials with high strength the cement mixture was additionally pressed at pressures 10, 20 and 30 MPa.

The pH was determined with an I-160M laboratory ion meter. The ratio of the mass of the charge to the mass of the physiological solution was 1 : 10. The measurements were performed after the samples had been kept in distilled water for 10, 60 and 240 min. A DRON-3M (CuK_α radiation, nickel filter) diffractometer was used for XPA in the angle range $2\theta = 20 – 70°$. The interpretation of the x-ray diffraction patterns was performed using the ASTM card files of diffraction certificates. A TESLA BS 340 scanning electron microscope with pre-deposited silver on a fresh cleavage face of a sample was used for electron-microscopic analysis in secondary electrons. A Mastersizer laser microanalyzer was used to determine the dispersity and specific surface area of the β-TCP particles and granules of amorphous and crystallized glass.

The open porosity was determined by a standard procedure on samples dried to constant mass at the 1st and 28th days. Kerosene was used as the saturating liquid. The resorption of the materials was studied in a SBF (Simulated Body Fluid) solution with pH = 7.2 over 7 days; CM : SBF = 1 g : 100 ml. The mechanical characteristics were studied by a standard procedure in a rupture machine at the 1st, 7th and 28th day; the samples were stored under moist conditions.

RESULTS AND DISCUSSION

The solubility of β-TCP fired at 900 and 1200°C in the process of crystallization of DCPD cement stone affects the pH of the contact medium (Fig. 1). The introduction of bioactive glass granules into the composition always increases the pH, to the highest degree for compositions containing crystallized glass. It was determined that the introduction in the system 900-0 of granules of bioactive glass increases pH from 4 to 5.2 (900 – 20a) and to 5.8 (900-20c) and in the system 1200-0 from 3 to 4.3 (1200-20a) and to 4.9 (1200-20c). Increasing the pH, on the one hand, has a posi-

[4] Here and below the content by weight, %.

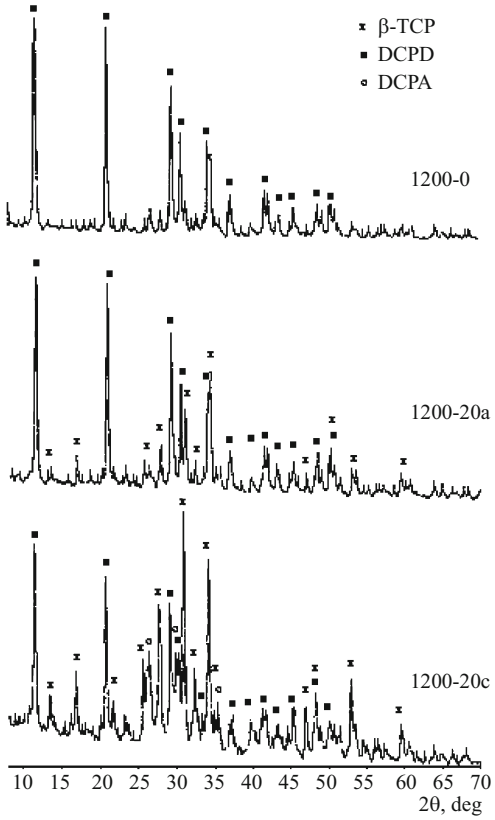

Fig. 2. X-ray diffraction patterns of compositions based on the high-temperature form of β-TCP: no filler (1200-0); with the introduction of 20% amorphous glass (1200-20a) and 20% crystallized glass (1200-20c).

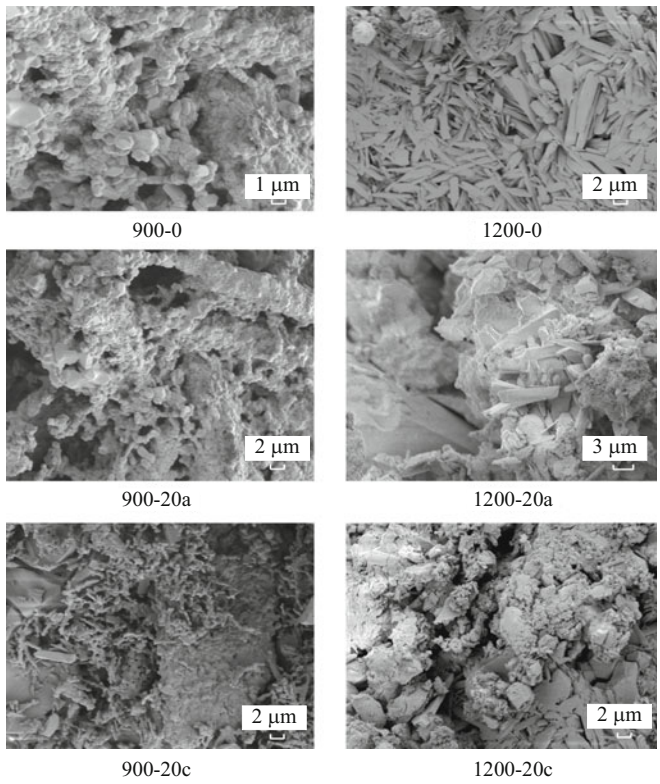

Fig. 3. Microstructure of pressed compositions based on low- and high-temperature β-TCP: no additives (900-0, 1200-0); with amorphous glass added (900-20a, 1200-20a); with crystallized glass added (900-20c, 1200-20c).

tive effect on the biological compatibility of composites and, on the other hand, decreases the reactivity of β-TCP and the rate of crystallization of the DCPD matrix.

X-ray phase analysis of the cement stone of the samples 900-0 and 1200-0 showed a single DCPD phase (Fig. 2). The DCPD phase in samples of composite materials with bioactive glass granules was basic, and peaks characteristic for the initial β-TCP phase and peaks due to dicalcium phosphate anhydride (DCPA) were also found. The crystallization process for the final DCPD phase in this case is sensitive to the acid-base character of the medium. It is evident from the x-ray diffraction patterns presented for the composites based on the high-temperature form of β-TCP that in samples with crystallized glass the intensity of the peaks characteristic for β-TCP (unreacted component) is higher than that of samples containing amorphous glass. This shows that the introduction of glass granules lowers the rate of crystallization of the desired phase of DCPD all the more strongly the higher the alkalinity of the glass. Similar dependences of the crystallization of DCPD are also observed for the low-temperature form of β-TCP.

The investigation of the microstructure of the pressed materials showed formation of DCPD crystals on the surface and in the pore space of the samples (Fig. 3). The microstructure of the 900-0 samples is represented by concretions of crystals smaller than 1 μm. When granules of glass are introduced into the composition (900-20a, 900-20c) fine DCPD crystals grow on the surface of the glass granules, covering them, and penetrate into the interior of the pore space with filamentary concretions forming. The DCPD crystals of the 1200-0 samples have a prismatic shape with size 4 – 10 μm along the long axis. When the glass granules are introduced the fraction of the prismatic DCPD crystals decreases and the presence of agglomerations of β-TCP crystals (1200-20a, 1200-20c) is observed in the interior of the sample.

On the 1st day the open porosity of the samples based on the high-temperature form of β-TCP is somewhat lower compared with the samples based on the low-temperature form of β-TCP; this is due to their lower water requirements. The porosity of the composite materials increases when glass granules are introduced into composition in the amounts from 14 to 22%. As the holding time of the samples in moist conditions increases, dicalcium phosphate dihydrate undergoes further crystallization in the interior of the composite sample and crystals penetrate into the pore space, which reduces the open porosity at the 28th day to 1 – 3% (Fig. 4).

The mechanical characteristics are presented in Figs. 5 and 6. Samples based on the high-temperature form of β-TCP

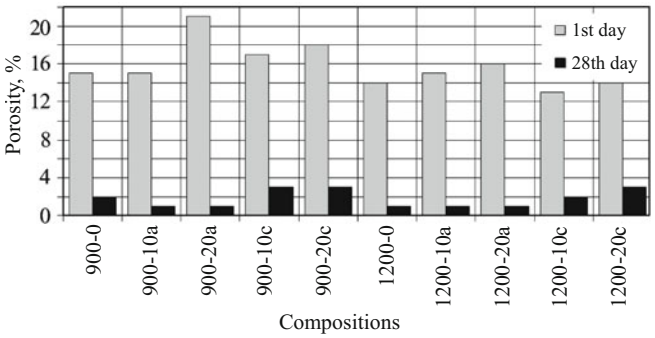

Fig. 4. Open porosity of the samples on the 1st and 28th days.

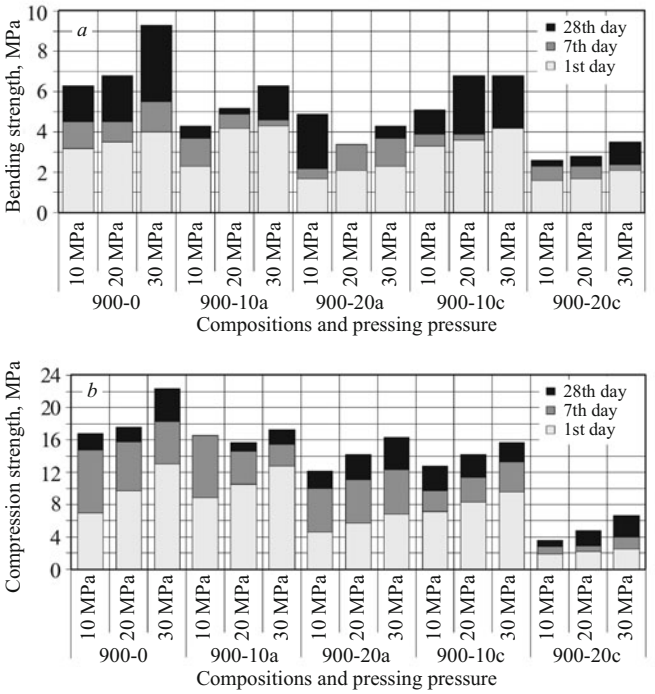

Fig. 5. Strength of the composite materials obtained from the low-temperature form of β-TCP with different pressing pressure: *a*) in bending; *b*) in compression.

(1200°C) and not containing glassy fillers possess higher porosity. This is explained, in the first place, by the smaller specific surface area of the high-temperature form of β-TCP compared with the low-temperature form and correspondingly by the lower moisture needs and porosity of the samples and, in the second place, by the fact that crystallization of DCPD in these samples occurs at the optimal pH of the medium — 3 – 4. Comparing the mechanical strength of the samples not containing fillers shows that as the pressing pressure increases from 10 to 30 MPa the primary compression strength increases from 18 to 20 MPa in the 1200-0 samples and from 7 to 13 MPa in the 900-0 series. The primary strength in bending of the 1200-0 samples is more than 2 time greater than analogous indicators for 900-0 samples.

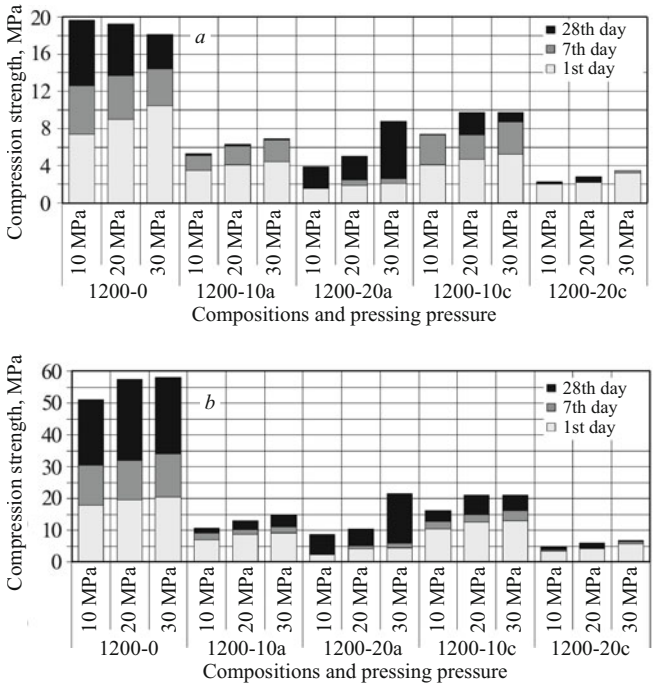

Fig. 6. Strength of the composite materials obtained from the high-temperature form of β-TCP with different pressing pressure: *a*) in bending; *b*) in compression.

As the holding time increases, further crystallization of the desired DCPD phase occurs, which more than doubles the strength compared with the primary strength of the samples.

In all samples, the introduction into the composite material of granules of bioactive glass leads to a proportional decrease of the bending and compression strength. In the series 900-0 samples, as the content of the granules of amorphous glass increases to 10 and 20% the strength in compression decreases by 10 – 25 and 40 – 50%, respectively. With increasing holding time the DCPD phase in the structure of the composition crystallizes, the porosity decreases and the strength increases. So, at the 28th day the strength in compression for 900-0, 900-10a and 900-20a samples is 16 – 23, 16 – 18 and 12 – 16 MPa depending on the pressing pressure. The following values of the strength in compression were obtained for the 900-0, 900-10c and 900-20c samples were obtained at the 28th day: 16 – 23, 13 – 16 and 4 – 7 MPa, respectively.

In the series of composite materials based on the high-temperature form of β-TCP the addition of granules of the amorphous and crystallized glasses in the amounts 10 and 20% results in a significant drop in the strength — by factors of 3 and 4. The strength in compression on the 1st day of the 1200-0, 1200-10a and 1200-20a samples is 18 – 20, 7 – 9 and 3 – 5 MPa, respectively, while on the 28th day it increases to 50 – 58, 11 – 14 and 9 – 21 MPa, respectively.

The strength in compression of the 1200-0, 1200-10c and 1200-20c samples is 18 – 20, 10 – 14 and 3 – 6 MPa, respectively, on the 1st day and 50 – 58, 16 – 21 and 4 – 7 MPa on

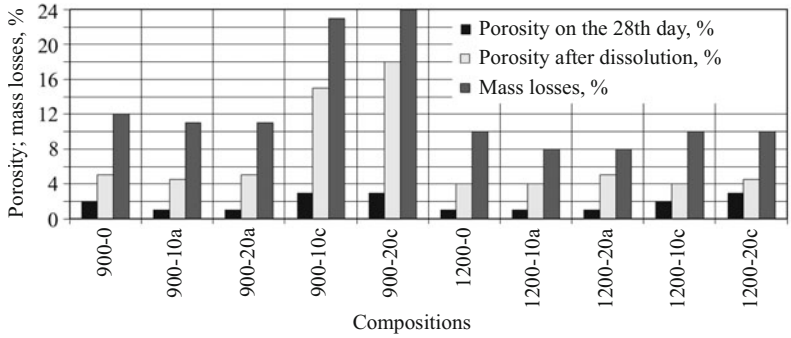

Fig. 7. Porosity and mass loss of samples held in the SBF solution for 7 days and pre-hardened for 28 days on a moist medium.

the 28th day. Thus, it was shown that the introduction of bioactive glass granules into the composition is desirable in amounts to 10% irrespective of the form of the initial β-TCP and the type of glass — amorphous or crystalline.

The resorption rate was determined for the composite materials obtained. The dependence of the change in the porosity and mass loss of the samples kept in the SBF solution is presented in Fig. 7.

The porosity of practically all samples after buffering (dissolution) for 7 days changes very little — in the range 4 – 5% (1 – 3% after 28 days of solidification); the mass losses are 8 – 12%. We presume that two mutually opposite processes are observed in the present case. First, as DCPD crystals dissolve, the contact medium becomes supersaturated with calcium and phosphate ions, which settle in the form of insoluble salts on the surface of the amorphous glass granules and, second, when granules of the crystallized glass are introduced into the 900-10c and 900-20c samples based on the low-temperature β-TCP the porosity is significantly higher, in the range 15 – 18%, and mass losses are 23 – 24%. This is due to the higher rate of dissolution of the DCPD crystals at alkaline pH as the glass dissolves.

In vivo investigations of the composites 1200-10c and 900-10c showed that they are biocompatible and osteointegrated. Partial resorption of the biocomposites with formation of osteoid tissue was observed 30 days after implantation.

CONCLUSIONS

Compositions based on dicalcium phosphate dihydride cement and filler — alkali bioactive glass (amorphous and crystallized) introduced in amounts to 20% — were studied. The optimal compositions were found to be 1200-10a, 1200-10c, 900-10a and 900-10c: strength in compression 12 – 20 MPa, pH 4.2 – 5.5, high resorption rate 8 – 20%. These materials are biocompatible and intensify new bone tissue formation, so that they can be used in different clinical cases.

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